REMARKS

Claims 1-37, 49-53 and 55 were pending in this application. Claims 12-17, 20, 21, 23-27, 53 and 55 are canceled herein as drawn to non-elected Groups. Applicants expressly reserve the right to pursue protection of any or all of the subject matter of the canceled claims in a subsequent application. Claims 4, 6, 9, 11, 28-31, 33, and 49 have been amended and new claims 57 and 58 have been added. Support for the claim amendments is discussed below, where necessary.

One paragraph of the specification has been amended to correct a clerical error. One replacement drawing sheet is provided, together with an annotated copy of Figure 4B showing the corrected labeling. Support can be found at least in the original Figure 4B as filed.

No new matter is introduced by any of these amendments.

After entry of this amendment **claims 1-11, 18, 19, 22, 28-37, 49-52, 57 and 58 are pending in this application**. Consideration of the pending claims is requested.

Election/Restriction

Applicants thank Examiner Nichols for withdrawing the restriction requirement between Groups i-iv, drawn to tags, targeting moieties, toxins, enzymes and fluorescent peptides. Applicants further thank Examiner Nichols for rejoining the nucleic acid sequence provisionally elected by the Applicants (SEQ ID NO: 36), together with the amino acid sequence encoded by it (SEQ ID NO: 37). Applicants acknowledge that the restriction requirement is otherwise made final.

Status of Application, Amendments and/or Claims

Applicants thank Examiner Nichols for entering the amendments identified in the Office action as Paper No. 6 (received by the Office on June 18, 2002), Paper No. 11 (received by the Office on January 14, 2003), and Paper No. 13 (received by the Office on March 28, 2003).

Drawings

The Office action notes (on page 3, paragraph 3) that "the labels on Figure 4B are overrun and unclear." Applicants provide a replacement Figure 4B with this Amendment. Applicants also provide an annotated version of the drawing sheet showing the corrections made to the Figure 4B labels. Applicants request that the objection be withdrawn.

Objection to the Specification

One paragraph of the specification has been amended to correct the misspelling identified in the Office action (at page 3, paragraph 4). Thus, Applicants request that this objection be withdrawn.

Claim Objections

All of the pending claims (claims 1-37, 49-53 and 55) have been objected to for allegedly reciting non-elected material. In conformance with the final restriction requirement set forth in the Office action at page 2, paragraph 1, claims have either been canceled (without prejudice) as containing non-elected subject matter or have been amended to recite the subject matter of elected Group I (drawn to a functional TGF-β family fusion protein, isolated nucleic acid molecule, vectors, and cells comprising the same), and recombined Groups Z (SEQ ID NO: 37) and Y (SEQ ID NO: 36). Thus, Applicants request that the claim objections be withdrawn.

***Claim Rejections under 35 U.S.C. §112, 1st paragraph*:**

Claims 10, 11, 14-17, 20-24, 31, 33, 49-53, and 55 have been rejected under 35 U.S.C. §112, 1st paragraph because the specification allegedly does not "enable any person skilled in the art . . . to make the invention commensurate in scope with these claims." Applicants traverse this rejection.

As an initial matter, claims 14-17, 20, 21, 23, 24, 53, and 55 have been canceled as drawn to non-elected groups or as redundant in light of other claim amendments. Thus, this rejection is moot with respect to these claims and should be withdrawn.

Claims 11, 31, 33 and 49-52 have been amended to recite, in relevant part, SEQ ID NO: 36 or SEQ ID NO: 37. The Office action states (at page 4, paragraph 6) that this subject matter is enabled. Thus, this rejection of these claims should be withdrawn.

Accordingly, the following discussion concerns the remaining rejection of claims 10 and 22. The Office action offers several justifications for this enablement rejection. All of these appear to be based on two general allegations: (i) claims to "substitutions, fragments, derivatives, and mutations" are allegedly over broad (see the action, page 4, paragraph 7; page 5, paragraph 11; and page 6, paragraph 12) and (ii) TGF-β family structural changes allegedly have unpredictable functional effects (see the action, page 4, paragraph 8; page 5, paragraph 9; page 6, paragraphs 13-14, page 7, paragraph 15, and page 8, paragraph 16) . Thus, the Office action concludes that a "large quantity of experimentation [is] necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity."

Both of claims 10 and 22 depend (directly or indirectly) from claim 1. Claim 1 has been amended to read as follows:

> 1. A functional TGF-β family fusion protein, comprising:
> a functionalizing peptide tag of no more than about 100 amino acids for detecting, quantifying or providing a specific additional function to the fusion protein; and
> a mature TGF-β family protein, or an amino acid sequence that has at least 95% sequence identity with the mature TGF-β family protein and which retains TGF-β family protein activity;
> wherein the functionalizing peptide tag is inserted between a pair of adjacent residues between about residues 1 and 22 of the mature portion of the TGF-β family protein;
> and wherein the activity of the TGF-β fusion protein is reduced by no more than 50% as compared to the mature TGF-β family protein.

The amendments to the language of claim 1 are supported, at least, at page 21, line 2, and at page 14, line 8 through page 16, line 3 of the original specification, and by original claim 14.

Basis (i) of Rejection of Claims 10 and 22:

Claims 10 and 22 did not (and do not) recite variations, derivations, fragments or substitutions except as incorporated from amended claim 1. Thus, if the specification enables ". . . an amino acid sequence, which has at least 95% sequence identity with the mature TGF-β family protein . . . ," then basis (i) of the enablement rejection of claims 10 and 22 should be withdrawn. Applicants believe that the specification fully supports and enables this scope, as discussed below.

The specification is enabling for TGF-β family proteins within the recited 95% sequence identity range. The Federal Circuit states that:

> [t]he test [for undue experimentation] is not merely quantitative, since *a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance* with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *Genentech, Inc.* v. *Novo Nordisk A/S*, 108 F.3d at 1365 (emphasis added).

At least because of the high level of skill in the art, only *routine* experimentation is required for one of skill in the art to make and use an amino acid sequence with 95% sequence identity with a mature TGF-β family protein. Though routine experimentation alone is sufficient to satisfy the enablement requirement, in this case, the specification also provides considerable guidance as to TGF-β family proteins within the 95% sequence identity range. For example, the TGF-β proteins shown in SEQ ID NOs: 8, 12, 32, 34, 36, and 38 are 97-99% identical to each other. In addition, the specification provides extensive guidance regarding how to determine sequence identity, *e.g.*, at page 19, line 26 through page 22, line 3, and how to produce and screen for active proteins having 95% sequence identity to TGF-β family proteins (*e.g.*, sections entitled "Variation of the Functionalized TGF-β Fusion Protein(s)" and "Activity of Functionalized TGF-β Family Fusion Proteins").

In light of the foregoing amendments and arguments, basis (i) of the §112, first paragraph rejection should be withdrawn against all claims.

Basis (ii) of Rejection of Claims 10 and 22:

The Office action generally contends that expressing TGF-β proteins and modifying TGF-β proteins is unpredictable. To support this contention, the Office action cites Han *et al.* (*Protein Expression and Purification*, 11:169-178, 1997), Qian *et al.* (*J. Biol. Chem*, 271(48):30656-30662, 1996), and Wakefield *et al.* (*Growth Factors*, 5:243-253, 1991). Applicants note that the Office action also cites Wolfraim *et al.* (*J. Immunol. Meth.*, 266(1-2):7-18, 2002), which is the Applicants' own publication published after the filing date of the application. Wolfraim *et al.* discusses the shortcomings of earlier works, such as Han *et al.* (see, *e.g.*, Wolfraim *et al.* at page 16, column 2, paragraph 2 of the Discussion), but otherwise does not stand for the proposition that expressing TGF-β proteins and modifying TGF-β proteins is unpredictable.

Each of the above-listed references teaches that mutations at the *C-terminus of TGF-β1* decrease TGF-β protein activity. However, none of the references other than Applicants' own work (Wolfraim *et al.* 2002) addresses structural/function relationships of other portions of a TGF-β family protein.

As discussed above, claims 10 and 22 (by virtue of the amendment to claim 1) recite: ". . . wherein the functionalizing peptide tag is inserted between a pair of adjacent residues between about residues 1 and 22 of the mature portion of the TGF-β family protein; . . . ." Among other things, Applicants appreciated (and were the first to exploit) that the N-terminal region of the mature TGF-β family proteins was relatively unconserved (see, *e.g.*, page 3, line 24; page 26, line 19; page 30, line 5 of the specification) and was, therefore, more tolerant of change (such as, by insertion of a tag).

Applicants have enabled TGF-β family proteins as recited in amended claims 1, 10 and 22. The specification describes *numerous* working examples of functionalized TGF-β family fusion proteins, including, *e.g.*, using TGF-β family proteins from two animal species, from three TGF-β family members, having two different peptide tags, and having tags insertion at various positions in the N-terminal region of these proteins. These many, broadly representative

examples together with the teaching of the specification enable one of skill in the art to make other members of the claimed genus *without undue experimentation.*

The Office action further contends that no functionalizing peptides other than the two reduced to practice by Applicants (*i.e.*, FLAG and HA tags) are enabled. The Office action supports this contention with references showing the *C-terminus* of TGF-β (or other *non-TGF-β family* proteins) is (are) prone to activity-destroying modification. Applicants recall MPEP §2164.02, which states:

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art . . . would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

Applicants have shown that the N-terminus of TGF-β the family proteins are tolerant of insertion of peptides as disclosed in the present application. Applicants' working examples demonstrate that the claimed functionalized TGF-β family fusion proteins comprising any functionalizing peptides can be made with routine experimentation. The Office action has not provided sufficient evidence to suggest otherwise. However, *only to facilitate prosecution*, Applicants have amended claim 1 (and therefore claims 10 and 22) to recite, in relevant part, ". . . a functionalizing peptide tag of no more than about 100 amino acids . . . ." This amendment is supported by the specification, at least, at page 14, line 13.

The Office action states (at page 5, paragraph 9) that the Office would find "small" peptides to be enabled. One hundred amino acids is a "small" peptide.

In view of the foregoing arguments and amendments, Applicants request that this rejection be withdrawn against all claims.

***Claim Rejections under 35 U.S.C. §102*:**

Claim 1 has been rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Jakowlew *et al.*, *Nucleic Acids Research*, 16(17):8730, 1988 ("Jakowlew"). Applicants traverse this rejection.

Jakowlew does not teach or suggest, among other things, a fusion protein or, in particular, a fusion protein comprising ". . . a functionalizing peptide tag of no more than about 100 amino acids for detecting, quantifying or providing a specific additional function to the fusion protein." Therefore, Jakowlew cannot anticipate amended claim 1, and Applicants request that this rejection be withdrawn.

Claims 1, 25, and 27-30 have been rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Hall *et al.*, WO 96/39430, published December 12, 1996 ("Hall I"). Applicants traverse this rejection.

Claims 25 and 27 have been canceled; therefore, this rejection is moot for these claims and should be withdrawn.

Claim 1 (and, therefore, dependent claims 28-30) has been amended to recite, in part, ". . . wherein the activity of the TGF-β fusion protein is reduced by no more than 50% as compared to the mature TGF-β family protein." This amendment is supported by the specification, for example, at page 14, line 19. Hall I does not teach or suggest this element of the amended claim. Nor does it enable one of ordinary skill in the art how to make such a fusion protein.

Hall I is alleged to teach "a fusion protein of TGF-β . . . that retains its biological activity." The TGF-β1 fusion protein of Hall I was expressible only in bacteria and had to be isolated under very harsh denaturing conditions from bacterial inclusion bodies. Not surprisingly, therefore, in Mv1Lu cell inhibition assays the "specific activity of the [Hall I] recombinant growth factor was ***considerably (~300 times) lower***" than TGF-β1 controls (see, Hall I at page 17, lines 15-16) (emphasis added). In addition, Hall I states (at page 23, line 5-6)

that "***no significant amount*** of stimulation of cell proliferation was observed" when the Hall I TGF-β1 fusion protein was applied to adherent NIH3T3 cells (emphasis added). Commercial TGF-β1 under the same conditions stimulated the proliferation of 3T3 cells approximately 15 fold (see, Hall I at page 23, lines 8-10). Thus, the Hall I constructs clearly did not retain anywhere near to wild type biological activity, and certainly not even 50% activity.

In stark contrast to Hall I, Applicants disclose functionalized TGF-β family fusion proteins that approximate (or exceed in some cases) wild-type TGF-β family protein activity. For example, Applicants tested certain embodiments of the disclosed fusion proteins in the same Mv1Lu cell inhibition assay used by Hall I. The specification states (at page 66, lines 6-7) "that the FLAG- and HA-tagged ligands were as efficient as the wild type molecule in inhibiting cell growth (FIG 7A)." Clearly illustrated in Figure 7A, at comparable concentrations to the wild type protein, N+5FLAG-TGF-β1 (SEQ ID NO: 17) (black bars) and N+5HA-TGF-β1 (SEQ ID NO: 21) (first set of grey bars) demonstrated between about 135% to 60% of wild type TGF-β1 protein activity (white bars).

Thus, a comparison between the Hall I and Applicants' Mv1Lu cell inhibition assay data, both compared to wild type protein, may be summarized as follows:

TGF-β Fusion Construct	**Construct Activity (relative units)**	**Wild Type Activity (relative units)**
Hall I	1 (*i.e.*, 300x lower)	300
Applicants' N+5FLAG-TGF-β1 (SEQ ID NO: 17)	409 (*i.e.*, 135% wt)	300
Applicants' N+5HA-TGF-β1 (SEQ ID NO: 21)	180 (*i.e.*, 60% wt)	300

Clearly, the Hall I fusion protein is comparatively inactive, while Applicant discloses fusion proteins that approximate wild type activity. Thus, Hall I does not teach or suggest a functionalized TGF-β1 family fusion proteins with the claimed level of activity.

In addition, as indicated in Applicants' later publication (Wolfraim *et al.* 2002, cited in the current Office action and discussed above for other reasons), continued characterization of Applicants' fusion proteins shows that they are at least as active as wild type versions of TGF-ß's in several biochemical and biological assays. This is clearly illustrated in Figure 2B-2E of Wolfraim *et al.* 2002, where the EC_{50} is calculated for two tagged constructs (N+5FLAG-TGF-ß1 at 30 pg/mL; N+5HA-TGF-ß1 at 35 pg/mL) and shown to be essentially identical to that calculated for the wild type recombinant TGF-ß1 (33 pg/mL) and wild type untagged TGF-ß1 (32 pg/mL).

Moreover, because the Hall I constructs retained so little activity ($1/300^{th}$ of wild type), Hall I actually teaches away from Applicants' invention. Hence, Hall I also does not render the claimed functionalized TGF-β1 family fusion proteins obvious.

In light of the foregoing amendments and arguments, Applicants request that this §102(b) rejection be withdrawn.

Claims 1-9, 12, 13, 18, 19, 25-30, 32, and 34-37 have been rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Hall *et al.*, U.S. Pat. No. 5,800,811, issued September 1, 1998 ("Hall II"). Applicants traverse this rejection.

According to Hall I, Hall II was the priority document for Hall I, and the two appear to be nearly identical disclosures. Hall II does not anticipate the pending claims for all the same reasons that Hall I does not anticipate the claims. Moreover, the Office action is mistaken when it concludes that Hall II "teaches that the tags included on the N-terminus of TGF-β1 . . . includes the 'pro-region' . . . ." Hall II expressly states (at column 2, lines 46-56) that "as used in [Hall II] transforming growth factor-β fusion protein means the ***active portion*** of TGF-β . . . . The ability to express and renature the active fragment of TGF-β in the ***absence of the pro-region***, in accordance with the [Hall II] invention . . . ." (emphasis added).

For all of the foregoing reasons, Applicants request that this §102(b) rejection be withdrawn.

Claims 1-9, 12, 13, 18, 19, 32, and 34-37 have been rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Purchio *et al.*, U.S. Pat. No. 5,221,620, issued June 22, 1993 ("Purchio"). Applicants traverse this rejection.

Claims 12 and 13 have been canceled; thus, this rejection is moot with regard to these claims and should be withdrawn.

As discussed above, claim 1 (and, therefore, dependent claims 2-9, 18, 19, 32 and 34-37) has been amended to recite, in relevant parts, "a functionalizing peptide tag of no more than about 100 amino acids for detecting, quantifying or providing a specific additional function to the fusion protein; . . . wherein the functionalizing peptide tag is inserted between a pair of adjacent residues between about residues 1 and 22 of the mature portion of the TGF-β family protein . . . ."

Purchio does not teach or suggest a functionalizing peptide tag, nor does it teach or suggest where such tag should be inserted to provide a functional TGF-β family fusion protein. Thus, Purchio does not teach or suggest all of the elements of the claim, and cannot anticipate the claims. Applicants request that this rejection be withdrawn.

In this rejection, Lee and McPherron, U.S. Pat. No. 5,827,733, issued October 27, 1998 ("Lee") is also mentioned. It is unclear whether Lee is intended to be cited in a separate §102(b) rejection, or if the Office action intended to raise an obviousness rejection combining the Purchio and Lee references. In either case, Lee does not anticipate the pending claims for the same reasons that Purchio does not anticipate the claims. Moreover, Lee does not make up for the deficiencies in Purchio and, therefore, the two references would not properly be combined in an obviousness rejection.

In light of the foregoing amendments and arguments, Applicants request that this (these) §102(b) and/or §103 rejection(s) be withdrawn.

Other Claim Amendments

Claim 9 has been amended to recite, in part, ". . . wherein the functionalizing peptide tag is inserted downstream of residue five of the mature TGF -ß family protein." This amendment is supported by the specification, at least, at page 29, line 7.

Newly Added Claims

The new claims are supported throughout the specification. In particular, language in new claim 57 ("mammalian TGF-ß isoforms") is supported at least at page 1, line 19. New claim 58 also is supported at page 11, lines 15-23. It is believed that the new claims meet all patent requirements, and are novel and non-obvious in light of all art currently of record.

CONCLUSION

It is respectfully submitted that the present claims are in a condition for allowance and such action is requested. If it may further allowance of the claims, the Examiner is invited to call the undersigned at the telephone number listed below.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By _____
Tanya M. Harding, Ph.D.
Registration No. 42,630

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 226-7391
Facsimile: (503) 228-9446